UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte GLORIA DECARLO MASSARO,
DONALD MASSARO and ROSHANTHA A. CHANDRARATNA

Appeal No. 2007-0852
Application No. 09/919,195
Technology Center 1600

Decided: August 28, 2007

Before DEMETRA J. MILLS, NANCY J. LINCK, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

The Appellants appeal the Examiner's Final Rejection of claims 13-28 for lack of written description. The claims are also rejected for anticipation and lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b) (2006).

We affirm.

Claim 13 reads as follows:

13. A method for the treatment or prevention of alveolar destruction in a mammal comprising the step of administering a therapeutically effective amount of an RARβ antagonist having specific RAR modulating activity to said mammal, and such antagonist is not specific to at least one other RAR receptor subtype.

Grounds of Rejection

1. Claims 13-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2. Claims 13-28 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

3. Claims 13-28 stand rejected under 102(b) as anticipated by Ghaffani, Cong, Xu, Wu, Song and Yu.

Cited References

Jun Yu et al., *Indirect effects of histamine on pulmonary rapidly adapting receptors in cats*, 79 Respiration Physiology 101-110 (1990).

Ching Song et al., *Ubiquitous receptor: A receptor that modulates gene activiation by retinoic acid and thyroid hormone receptors*, 91 Proc. Natl. Acad. Sci. USA 10809-10813 (1994).

Qiao Wu et al., *Modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and their heterodimerization*, 16 (7) The EMBO Journal 1656-1669 (1997).

Xiao-Chun Xu et al., *Suppression of Retinoic Acid Receptor ß in Non-Small-Cell Lung Cancer In Vivo: Implications for Lung Cancer Development*, 89 (9) Journal of the National Cancer Institute 624 (1997).

Cong Yan et al., *Retinoic acid-receptor activation of SP-B gene transcription in respiratory epithelial cells*, 275 The American Physiological Society L239-L246 (1998).

Manely Ghaffari et al., *Inhibition of hSP-B promoter in respiratory epithelial cells by a dominant negative retinoic acid receptor*, 276 The American Journal of Physiology L398-L404 (1999).

DISCUSSION

Background

The present invention is directed to methods and compositions for promoting the formation of alveoli in mammalian lung tissue. (Specification 4.) In one embodiment, the invention comprises a therapeutic method for inducing the formation of alveoli in mammalian lung tissue by administration of a composition comprising a therapeutically effective amount of a ligand that is an RAR (retinoic acid receptor) β antagonist. (Specification 4-5.) The retinoid receptors are part of the steroid/thyroid/vitamin D superfamily of nuclear receptors. (Specification 8.) In a preferred aspect of this embodiment, the RAR β receptor antagonist or inverse agonist has specific RAR modulating activity at the RAR receptor, and is not specific to the RARα receptor. (Specification 6-7.)

By "specific RAR modulating activity" in the claim, it is meant that such a compound has a disassociation constant (KD) (the ligand concentration at which 50% of the RAR receptors are complexed with the ligand) at an RAR receptor at least 10 times, preferably at least 25 times, even more preferably at least 50 times,

and most preferably at least 100 times greater than the K_D for the binding of the same ligand to an RXR receptor. (Specification 5.)

The term "antagonist" is defined in the Specification to mean a retinoid receptor ligand that will inhibit the activation of transcription by the retinoid receptor at a gene having an appropriate retinoid receptor response element in the presence of an agonist of the retinoid receptor. (Specification 6.).

The term "agonist" means a retinoid receptor ligand that will cause the activation of transcription at a gene having an appropriate retinoid receptor response element. *Id.*

Written Description

1. Claims 13-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. We select claim 13 as representative of the rejection before us.

The Examiner contends the claims lack written description because the "scope of the claims is unknown due to the structure limitations not being specifically disclosed." (Answer 4.)

Appellants acknowledge there is no structural limitation for the compounds that can be used in the method in the claims, but contend that the "description of the required biological [and] pharmaceutical properties is sufficient as an enabling disclosure. (Br. 7.)

Appellants particularly argue that the Specification on page 5, line 25, through page 6, line 6 describes assays by which the specific RAR modulating activity of a compound can be routinely determined. (Br. 10-

11). Appellants further argue that the Specification on page 12, line 30 to page 13, line 8 incorporates by reference 4 patents, each of which describes the synthesis of RAR ligands having antagonist and/or inverse agonist activity. (Br. 11.)

The Appellants argue that "the specification provides one exemplary compound of specific structure as a working example but the compounds incorporated by reference [in the application] provide a multitude of additional working examples." [Emphasis original.] (Br. 12.)

We find that Appellants have not described the subject matter of claim 13 in a manner to evidence that Appellants were in possession of the claimed invention as of the filing date of the application. While Appellants rely on a specific structure in the Specification as the claimed RARβ antagonist, the only structure present in the Specification is found on page 16. The compound is described on pages 15-16 of the Specification as having "RARβ agonist activity." Appellants have provided a specific definition of the term "antagonist" in the Specification and have not indicated how the compound described in the Specification at pages 15-16 as an "agonist" meets the definition of "antagonist", as claimed. Thus the Specification is devoid of any structure of any compound which meets the definition of an "antagonist" within the scope of claim 13.

The Specification also refers to certain patents which are characterized as disclosing "ligands having antagonist and/or inverse agonist activity" (Specification 13: 1-5). We also do not find this disclosure sufficient to satisfy the written description requirement. The antagonist is further defined in claim 13 as being "not specific to at least one other RAR receptor subtype." Appellants contend that the patents "list numerous

exemplary compounds of specific disclosed structure" (Br. 11), but they have not provided evidence that the cited patents describe antagonists which are also not specific to at least one other RAR receptor subtype as recited in claim 13.

In *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), the court held that claims generically reciting cDNA encoding vertebrate or mammalian insulin were not adequately described by the disclosure of cDNA encoding rat insulin. *Id.* at 1568, 43 USPQ2d at 1406. The court held that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

Id. At 1569, 43 USPQ2d at 1406. The court held that a

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Id. The court has since clarified that the complete structure of the representative species does not necessarily have to be described. *See Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956, 964-65, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

The instant Specification does not adequately describe the recited genera of compounds having RARβ antagonist activity for use in the claimed method. The *Eli Lilly* court held that a fully described genus is one for which a person skilled in the art can "visualize or recognize the identity of the members of the genus." Here,

as the Examiner has pointed out, the Specification does not provide guidance regarding what chemical compounds are responsible for RARβ antagonist activity, such that a person skilled in the art can "visualize or recognize the identity of the members of the genus.

Thus, the Specification does not describe the recited genera of RARβ antagonist compounds sufficiently to allow a person skilled in the art to determine which compounds possess the required antagonist activity.

The court confronted similar facts in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004). In that case, the patent claimed a method of selectively inhibiting the enzyme PGHS-2 (also known as COX-2) by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human." *Id.* at 918, 69 USPQ2d at 1888. The patent "describe[d] in detail how to make cells that express either COX-1 or COX-2, but not both . . . , as well as 'assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product.[']" *Id.* at 927, 69 USPQ2d at 1895.

The court held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: Without disclosure of *which* peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims were not adequately described. *See id.* ("As pointed out by the district court, . . . the '850 patent does not disclose just 'which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.' . . . Without such disclosure, the claimed methods cannot be said to have been described.").

Appellants argue that one of ordinary skill in the art could use the assay methods described in the patents mentioned in the Specification to test compounds described in the patents incorporated by reference into the Specification at page 13. However, this disclosure also fails to provide an adequate written description of compounds meeting the definition of "antagonist" set forth in the specification and as recited in claim 13.

Just as in *University of Rochester*, the present application claims a genus of chemical compounds (RARβ antagonists having specific modulating activity and not specific to at least one other RAR receptor subtype) for use in the claimed method. However the Specification fails to describe which compounds have this antagonist function. The screening assays present in the patents incorporated by reference into the Specification are insufficient to show Appellants were in possession of compounds having RARβ antagonist activity.

In view of the above, the written description rejection of the claims is affirmed.

Enablement

2. Claims 13-28 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. We select claim 13 as representative of this rejection since the claims are not separately argued by Appellants.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). "The key word is 'undue,' not 'experimentation.'" *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Given the Specification does not describe any compound known to have the claimed RARβ antagonist activity, it also fails to enable the claimed method for the treatment or prevention of alveolar destruction in a mammal comprising the step of administering a therapeutically effective amount of an RARβ antagonist having specific RAR modulating activity to said mammal, and such antagonist is not specific to at least one other RAR receptor subtype.

While we acknowledge that the Specification provides evidence that RAR antagonists were known in the prior art, we find no evidence of RAR antagonists that meet the claimed requirement of being "not specific to at least one other RAR receptor subtype." Thus, even if methods of determining which compounds meet this limitation were known in the art, absent even a single working example, it is our opinion that it would require undue experimentation to carry out the full scope of the claim. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In this case, because no evidence has been presented that RAR antagonists with the claimed characteristics have been identified or even exist, it is clearly unpredictable that compounds within the scope of claim 13 could be found.

While Appellants rely on a specific structure in the Specification, the only structure present in the Specification is found on pages 15-16, (Br. 10-11.). The compound described on pages 15-16 of the Specification is stated as having "RARβ agonist activity."[1] Appellants have provided a specific definition of the term "antagonist" in the Specification and have not indicated how the compound described in the Specification at pages 15-16 as an "agonist" meets the definition of "antagonist", as claimed.

While Appellants argue that the Specification discloses assays by which the specific RAR modulating activity of a compound can be routinely determined, we find it would require undue experimentation to determine which compounds possess the claimed characteristics of an antagonist as defined throughout the Specification. The claimed antagonist must be a retinoid receptor ligand that will inhibit the activation of transcription by the retinoid receptor at a gene having an appropriate retinoid receptor response element in the presence of an agonist of the retinoid receptor. In addition the antagonist must be a compound having a disassociation constant (KD) (the ligand concentration at which 50% of the RAR receptors are complexed with the ligand) at an RAR receptor at least 10 times greater than the K_D for the binding of the same ligand to an RXR receptor (Specification 5). The antagonist must be selected so that it is not specific to at least one other RAR receptor subtype. Since Appellants have described no compounds having the claimed antagonist activity, it would require undue experimentation to discern them.

[1] We note that the Examiner states that the only compounds which "fit within the bounds of the instant claim 13 are the compounds/method of the US Patent #6,303,648" (Answer 5). This application is a continuation of the cited patent. The compound is described in this patent application as an agonist (Spec. 15-16), not as an antagonist as claimed.

Thus, the Specification is devoid of any structure of any compound which meets the definition of an "antagonist" within the scope of the claim, and one of ordinary skill in the art would not have been able to practice the claimed method without knowledge of such a compound.

The lack of enablement rejection is affirmed.

Anticipation

Claims 13-28 stand rejected under §102(b) as anticipated by Ghaffani, Cong, Xu, Wu, Cao, Song and Yu. We select claim 13 as representative of this rejection since the claims are not separately argued by Appellants.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997).

> Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939), *quoted with approval in In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)(internal citations omitted). Thus, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. *See id.; Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the

claimed limitations, it anticipates. *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986).

The Examiner finds:

> Ghaffari discloses compounds that . . . RAR modulation that affects the lung. Cong discloses RAR modulation in its role in the development of the lung. Xu discloses modulation of RAR for lung problems. Wu discloses RAR modulation in lung problems. Cao discloses RAR modulation in the lung tissue. Song discloses RAR modulation in the lung tissue. Yu teaches RAR modulation and its link to the lungs. These all teach RAR modulation and lung tissues. These compounds would inherently encompass the instantly claimed invention.

(Answer 9).

Appellants contend that none of the cited references discloses all the claimed elements or limitations. (Br. 16). Appellants further argue

> these claims require in the method of treatment or prevention the use of a compound that is an RARβ antagonist, and not a modulator of RXR receptors. (see the definition of "specific RAR modulating activity" on page 5 lines 17 - 24 of the specification) nor a modulator of either RARα or RARγ receptors. . . . The Examiner asserts that these elements must be inherent in the compounds used in the references. For the reason explained below the assertion of inherency is in serious error. There is a significant difference between just being a "retinoid", namely a compound having some modulating activity on any or all retinoid receptors and being selective to RAR receptors (not active on RXR receptors) and then being further selective by acting as an antagonist of RARß and being inactive on either RARα or RARγ receptors.

(Br. 16).

We agree with Appellants that the Examiner has failed to set forth a prima facie case of anticipation based on inherency. The claims require administering an RARβ antagonist having specific RAR modulating activity to said mammal in an

amount effective to treat or prevent alveolar destruction. They further require that such antagonist not be specific to at least one other RAR receptor subtype. The term "antagonist" is defined in the Specification to have a very specific meaning, i.e., a retinoid receptor ligand that will inhibit the activation of transcription by the retinoid receptor at a gene having an appropriate retinoid receptor response element in the presence of an agonist of the retinoid receptor. (Specification 6).

The Examiner has failed to show or explain where any of the cited references disclose using an effective amount of an RARβ antagonist to treat or prevent alveolar destruction. If such a teaching had been identified, then perhaps the doctrine of inherency could be relied upon to shift the burden to Appellants to show such a prior art RARβ antagonist was not specific to at least one other RAR receptor subtype. But that is not the case here. (*See* Answer *passim*.)

In view of the above, the anticipation rejections are reversed.

CONCLUSION

The written description and lack of enablement rejections of claims 13-28 are affirmed. The anticipation rejections are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc

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